77

Double-Blind Comparison of Escitalopram and Duloxetine in the Acute Treatment of Major Depressive Disorder

Jeff Jonas, MD;[1] Anjana Bose, PhD;[1] George Alexopoulos, MD;[2] Carl Gommoll, MS;[1] Dayong Li, PhD;[1] Chetan Gandhi, PhD[1] I

[1]Forest Research Institute, Jersey City, NJ; [2]Weill Medical College of Cornell University, New York, NY Sponsor: George S. Alexopoulos, MD

Abstract

Introduction: Previous studies have demonstrated that the selective serotonin reuptake inhibitor (SSRI) escitalopram has comparable or greater efficacy and better tolerability than the serotonin-norepinephrine reuptake inhibitor (SNRI) venlafaxine XR. The present study evaluates the efficacy and safety of escitalopram 10-20 mg/day versus another SNRI, duloxetine 60 mg/day, in the acute treatment of patients with moderate to severe major depressive disorder (MDD). Dosing was consistent with the FDA-approved package insert of both drugs.

Methods: Outpatients (aged 18-80 years) with DSM-IV diagnosed MDD (Montgomery-Asberg Depression Rating Scale [MADRS] total score ≥26) were randomized to 8 weeks of double-blind treatment with escitalopram 10-20 mg/day (dose fixed at 10 mg/day for the first 4 weeks with optional up-titration to 20 mg/day thereafter) or duloxetine 60 mg/day. The primary efficacy endpoint was change from baseline at week 8 in MADRS total score using the last observation carried forward (LOCF) approach.

Results: Significantly more patients discontinued during 8 weeks of treatment in the duloxetine group (n=41/133) than in the escitalopram group (n=18/137), 31% vs. 13% (p=0.001), respectively. Mean baseline MADRS total scores were 31.0 for the escitalopram group and 31.6 for the duloxetine group. At week 8, escitalopram treatment resulted in significantly greater improvement compared with duloxetine on the prospectively-defined primary efficacy endpoint of change from baseline in MADRS total score using the LOCF approach (LSMD -2.42 [95% CI: -4.73, -0.11]; p=0.040). Moreover, the proportion of patients responding to escitalopram treatment (50% improvement in MADRS total score) was significantly greater in the escitalopram group than in the duloxetine group, 68% versus 52% (p=0.011; LOCF), respectively. Remission (MADRS ≤10) rates were 44% in the escitalopram group and 38% in the duloxetine group. Escitalopram was better tolerated; significantly fewer escitalopram-treated patients discontinued due to adverse events compared with duloxetine (2% versus 13%; p=0.001). Serious adverse events were reported in 1 escitalopram-treated patient (1%) and 5 duloxetine-treated patients (4%) during the 8-week treatment period.

Conclusions: These findings suggest that escitalopram is better tolerated and more effective than duloxetine in the treatment of MDD. These results, along with those from comparative studies with venlafaxine XR suggest that escitalopram has equal or greater efficacy in the treatment of MDD compared to SNRIs.

Introduction

- Previous studies have demonstrated that the selective serotonin reuptake inhibitor (SSRI) escitalopram has comparable efficacy and better tolerability than the serotonin-norepinephrine reuptake inhibitor (SNRI) venlafaxine XR in the treatment of major depressive disorder (MDD).[1,2]
- This study evaluated the efficacy and safety of escitalopram 10-20 mg/day versus another SNRI, duloxetine 60 mg/day, in the acute treatment of patients with moderate to severe MDD.
  - Escitalopram is the most selective SSRI binding at the serotonin transporter studied to date[3]
    - 10 mg/day is the recommended starting and maintenance dose; 10-20 mg/day is the therapeutic dose range[4-6]
  - Duloxetine is an SNRI[7]
    - 60 mg/day is the recommended starting and therapeutic dose[8-12]

Methods

Patient Population

- Male or female outpatients, 18-80 years of age, meeting DSM-IV criteria for MDD with a current depressive episode of at least 12-weeks duration.
- A Montgomery-Asberg Depression Rating Scale (MADRS) total score ≥26 and a minimum score of 4 on the Clinical Global Impressions of Severity (CGI-S) Scale.

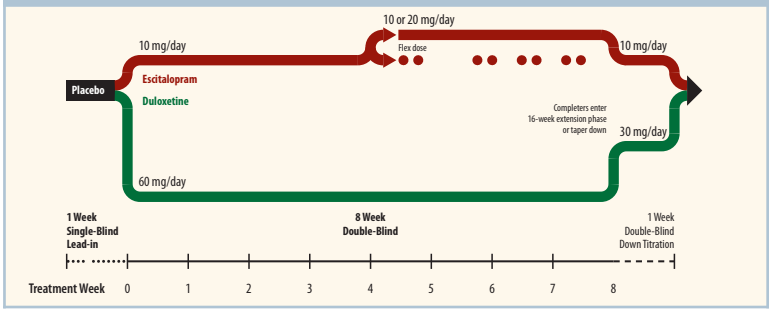
Study Design

- Randomized, 8-week, double-blind, multicenter, parallel-group study (Figure 1)
  - Escitalopram 10 mg/day for the first 4 weeks, 10-20 mg/day thereafter (2-3 capsules)
  - Duloxetine 60 mg/day (2-3 capsules)
  - Dosing was consistent with FDA-approved package insert of both drugs
  - Completers had the option to enter a 16-week double-blind extension study or enter a down-taper period and leave the study
- The prospectively defined primary efficacy variable was change from baseline to end of week 8 in MADRS total score using the last observation carried forward (LOCF) approach.

Statistical Analyses

- The safety population was defined as all patients who received at least 1 dose of double-blind study medication.
- The intent-to-treat (ITT) population was defined as all patients in the safety population with at least 1 valid postbaseline assessment of MADRS.
- Baseline imbalance was tested using an analysis of variance (ANOVA) model with treatment and study center as factors for continuous variables, and Cochran-Mantel-Haenszel (CMH) tests controlling for study center for categorical variables. The percentage of patients prematurely discontinuing from the study was analyzed using the Fisher exact test.
- Statistical analyses were conducted using the LOCF approach with the observed cases (OC) approach used in supportive analyses.
- Efficacy analyses were performed using an ANCOVA model with treatment group and study center as factors and baseline score as a covariate.
  For Clinical Global Impressions of Improvement (CGI-I), baseline CGI-S score was used as a covariate. Prospectively defined response (CGI-I ≤ 2, 50% improvement from baseline in MADRS scores, 50% improvement from baseline in $HAMD_{24}$ score) and remission (MADRS ≤10, or $HAMD_{17}$ ≤ 7) criteria were analyzed using logistic regression with treatment group and baseline score as explanatory variables.

Figure 1. Study Design



Results

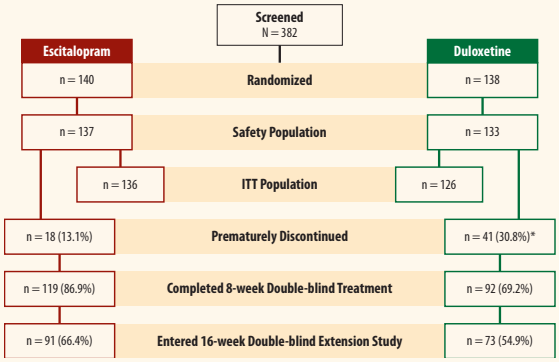
Patient Disposition

- The study was completed by 211 of 278 patients (78.1%) who met study eligibility criteria (382 patients screened) and were randomized to receive treatment with escitalopram 10-20 mg/day or duloxetine 60 mg/day (Figure 2).
- Significantly more patients in the duloxetine group discontinued during 8 weeks of treatment than in the escitalopram group (Figure 3; 31% vs. 13%, $p<0.01$). The most common reason for discontinuation in the duloxetine group was adverse events followed by withdrawal of consent; the rates for both were statistically significantly higher than for escitalopram.

Demographics and Baseline Patient Characteristics

- Baseline demographics and clinical characteristics were generally similar between treatment groups and are summarized in Table 1. There were no clinically meaningful differences between treatment groups at baseline in terms of disease severity, course of illness, or previous treatment for depression.
- Patients in both groups were moderately to severely ill at baseline with mean MADRS scores of 31 to 32.

Figure 2. Patient Disposition



**$p<0.01$

Table 1. Patient Demographics (Safety Population)

Characteristic	Escitalopram (n = 137)	Duloxetine (n =133)
Age (yrs), mean ± SD	41.8 ± 12.7	43.0 ± 13.4
Female, n (%)	81 (59.1)	85 (63.9)
White, n (%)	108 (78.8)	108 (81.2)
Baseline MADRS score, mean ± S.E.M. (ITT Population)	31.0 ± 0.32	31.6 ± 0.34
Baseline CGI-S score ,mean ± S.E.M. (ITT Population)	4.5 ± 0.05	4.5 ± 0.05

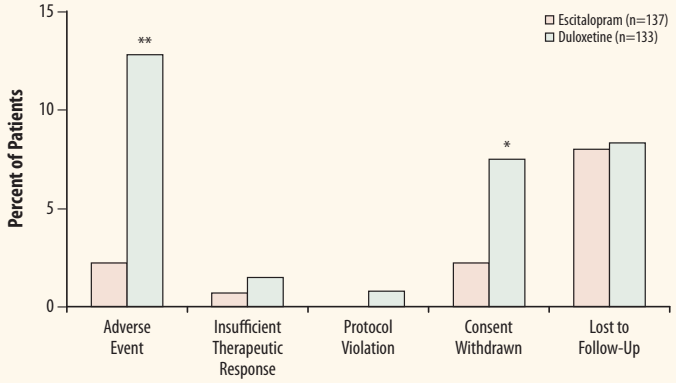
Dosing

The overall mean dosage for escitalopram was 13.0 mg/day. No upward dosing adjustments were made in approximately half the patients (44.5% escitalopram vs. 53.4% duloxetine).

Efficacy Analyses

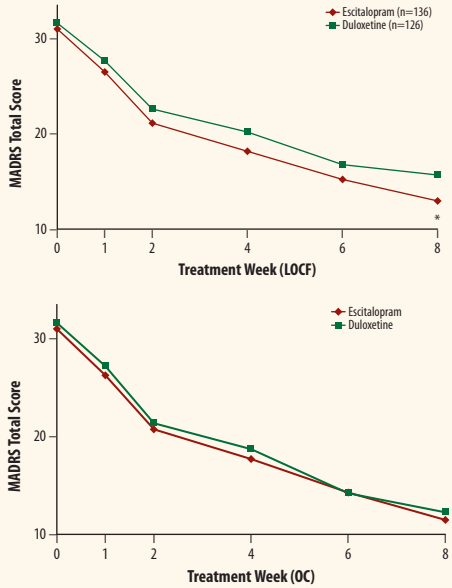
- At week 8, escitalopram treatment resulted in significantly greater improvement compared with duloxetine on the prospectively defined primary efficacy variable of change from baseline in MADRS total score using the LOCF approach (Figure 4a; -18.5 escitalopram versus -16.1 duloxetine, LSMD -2.4, $p=0.040$).

Figure 3. Reasons for Discontinuation



$p<0.05$ **$p<0.01$

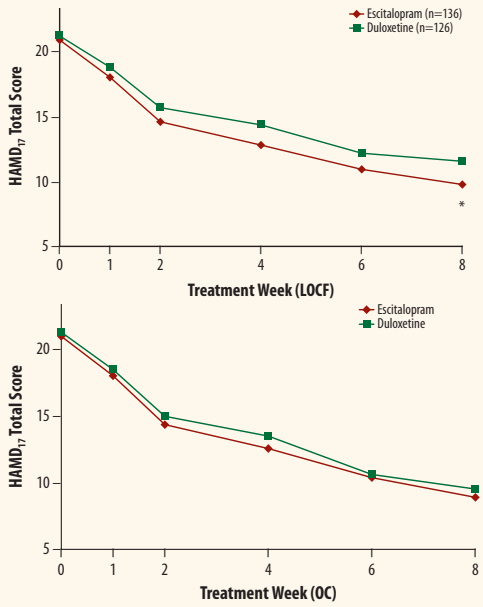
Figure 4. MADRS Mean Score by Visit, LOCF (4a) and OC (4b) (ITT Population)



*$p \leq 0.05$

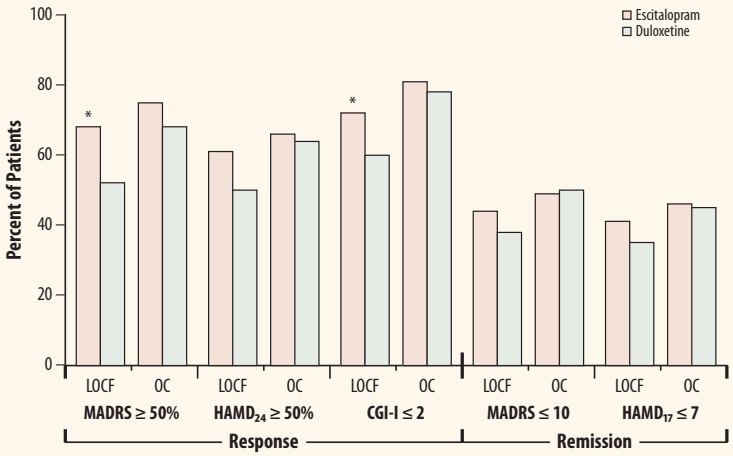
- Analysis of patients completing 8 weeks of treatment using the OC approach showed no difference between treatment groups (Figure 4b; -19.5 escitalopram versus -19.2 duloxetine, LSMD -0.3, $p=0.79$).
- In addition, escitalopram treatment resulted in significantly greater improvement compared with duloxetine on change from baseline at week 8 in HAMD17 score using the LOCF approach (Figure 5a). There was no difference between treatment groups in the analysis of patients completing 8 weeks of treatment using the OC approach (Figure 5b).

Figure 5. $HAMD_{17}$ Mean Score by Visit, LOCF (5a) and OC (5b) (ITT Population)



- The proportion of patients responding to treatment and the remission rates for the escitalopram and duloxetine treatment groups are presented in Figure 6.

Figure 6. Response and Remission Rates at Endpoint (LOCF) and Week 8 (OC) (ITT Population)



*p<0.05

Escitalopram 10-20 mg/day was at least as effective as duloxetine 60 mg/day on the primary and additional efficacy parameters based on the LOCF and OC approach (Table 2).

Table 2. Additional Efficacy Variables: Change from Baseline to Week 8 (Mean ±S.E.M.) LOCF and OC (ITT Population)

	Change at Week 8 from Baseline, Mean ± S.E.M.			
	LOCF		OC	
Scale	Escitalopram (n=136)	Duloxetine (n=126)	Escitalopram (n=110)	Duloxetine (n=91)
HAMD24	-14.5 ± 0.75	-12.7 ± 0.85	-15.6 ± 0.79	-15.5 ± 0.92
HAMD Item 1: Depressed Mood	-1.7 ± 0.09	-1.5 ± 0.11	-1.8 ± 0.10	-1.8 ± 0.11
HAMD Subscales				
Melancholia subscale	-6.6 ± 0.35	-5.7 ± 0.37	-7.2 ± 0.36	-6.8 ± 0.41
Psychomotor retardation	-4.3 ± 0.24	-3.7 ± 0.25	-4.6 ± 0.25	-4.5 ± 0.27
Cognitive disturbance	-2.3 ± 0.16	-2.1 ± 0.20	-2.3 ± 0.17	-2.5 ± 0.23
Sleep disturbance	-1.7 ± 0.16*	-1.4 ± 0.19	-1.9 ± 0.16	-1.7 ± 0.22
CGI-I	2.1 ± 0.09	2.3 ± 0.11	1.9 ± 0.09	1.9 ± 0.10
CGI-S	-2.0 ± 0.10	-1.7 ± 0.12	-2.2 ± 0.11	-2.2 ± 0.13
HAMA	-7.5 ± 0.53	-7.6 ± 0.60	-7.9 ± 0.58	-9.0 ± 0.58
QoL	12.2 ± 1.0	10.6 ± 1.12	13.8± 1.08	12.6 ± 1.23

*p<0.05

- Post hoc analysis indicated that escitalopram 10-20 mg/day was at least as effective as duloxetine 60 mg/day on HAMD Somatic items based on the LOCF and OC approach (Table 3).

Table 3. HAMD Somatic Items (post hoc analysis): Change from Baseline to Week 8 (Mean ± S.E.M.) LOCF and OC (ITT Population)

	Change at Week 8 from Baseline, Mean ± S.E.M			
	LOCF		OC	
	Escitalopram (n=136)	Duloxetine (n=126)	Escitalopram (n=110)	Duloxetine (n=91)
HAMD Somatic Items				
Item 11: Somatic Anxiety	-0.53 ± 0.09	-0.50 ± 0.09	-0.55 ± 0.10	-0.70 ± 0.10
Item 12: Somatic Symptoms–GI	-0.33 ± 0.05	-0.41 ± 0.06	-0.32 ± 0.06	-0.48 ± 0.07
Item 13: Somatic Symptoms–General	-0.79 ± 0.07	-0.70 ± 0.07	-0.84 ± 0.08	-0.80 ± 0.09

Safety Analysis

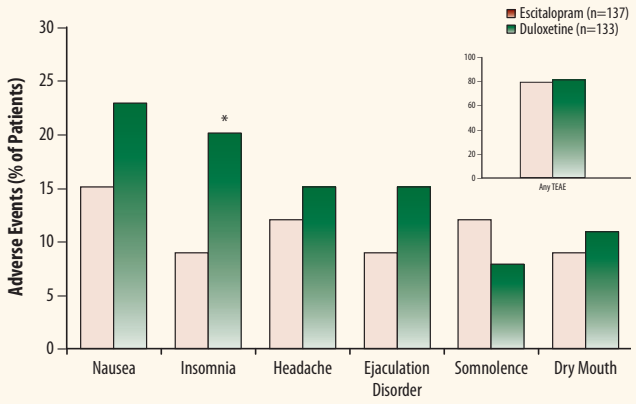
- Serious adverse events were reported in 1 escitalopram-treated patient (1%) and 5 duloxetine-treated (4%) patients during the 8-week treatment period.
  - The escitalopram-treated patient reported the following serious adverse events:
    - –Fall and back pain
  - The duloxetine-treated patients reported the following serious adverse events:
    - –Chest discomfort
    - –Hypertensive crisis
    - –Anxiety, depression
    - –Depression, mental disorder
    - –Accidental overdose
- A summary of adverse events leading to treatment discontinuation, with a breakdown according to time on drug, is presented in Table 4.

Table 4. Adverse Events Leading to Treatment Discontinuation (Safety Population)

	Escitalopram (n=137)	Duloxetine (n=133)
Prematurely Discontinued Due to Adverse Events	3 (2.2%)	17 (12.8%)
Days on Drug	**Adverse Event, n**	
≤7 days	3 • headache • panic disorder • lethargy	11 • nausea (2) • palpitations • depersonalization • stomach discomfort/nervousness • vomiting • mucosal dryness/anxiety • hydriasis/nausea/ vomiting/trimus • confusional state • depression • diarrhea/dry mouth/ nausea/ ejaculation failure
8 to 14 days	0	4 • depression/mental disorder • nausea • insomnia • accidental overdose/anxiety/depression
15 to 21 days	0	1 • rash papular
22 to 28 days	0	1 • hypertension/hypertensive crisis

- Treatment-emergent adverse events were reported by 80% of patients in each treatment group. The most frequent treatment-emergent adverse events, occurring in at least 10% of patients in either treatment group, are shown in Figure 7.

Figure 7. Most Frequent (≥10% of Patients in Either Treatment Group) Treatment-Emergent Adverse Events (Safety Population)



*$p<0.05$

Conclusions

- Escitalopram was statistically significantly superior to duloxetine on the primary efficacy variable of change from baseline in MADRS total score using the LOCF approach.
- In the analysis of patients completing the 8-week study using the OC approach, escitalopram and duloxetine treatment resulted in comparable improvements in MADRS total score
- Escitalopram and duloxetine had comparable rates of response and remission.
- Escitalopram was significantly better tolerated than duloxetine.
- The present findings indicate that escitalopram is better tolerated and at least as effective as the SNRI duloxetine in the treatment of MDD.
- These results are similar to those from comparative studies of escitalopram with the SNRI venlafaxine XR.

References

1. Bielski RJ,Ventura D, Chang CC. J Clin Psychiatry. 2004;65: 1190 - 1196.
2. Montgomery SA,Huusom AK, Bothmer J. Neuropsychobiology. 2004;50:57 - 64.
3. Owens MJ, Knight DL,NemeroffCB. Biol Psychiatry. 2001;50: 345 - 350.
4. Wade AG,Michael Lemming O, Bang Hedegaard K. Int Clin Psychopharmacol. 2002;17:95 - 102.
5. Burke WJ,Gergel I, Bose A. J Clin Psychiatry. 2002;63:331 - 336.
6. Lexapro package insert.
7. Karpa KD, Cavanaugh JE, Lakoski JM. CNS Drug Rev. 2002; 8:361 - 376.
8. Mallinckrodt CH, Prakash A,Andorn AC,Watkin JG,Wohlreich MM. J Psychiatr Res. 2006;40:337 - 348.
9. Mallinckrodt CH,Goldstein DJ,Detke MJ, Lu Y,Watkin JG, Tran PV. Prim Care Companion J Clin Psychiatry. 2003;5:19 - 28.
10. Detke MJ, Lu Y,Goldstein DJ,McNamara RK,Demitrack MA. J Psychiatr Res. 2002;36:383 - 390.
11. Detke MJ, Lu Y,Goldstein DJ,Hayes JR,Demitrack MA. J Clin Psychiatry. 2002;63:308 - 315.
12. Cymbalta package insert.

Supported by Forest Laboratories, Inc.
Presented at the 45th Annual Meeting of the American College of Neuropsychopharmacology
December 3 – 7, 2006 | Hollywood, FL